SECTION II
REMARKS

Regarding the Amendments

Claims 20, 21, 22, 24, 26, and 27 have been amended as set forth in the above Complete Listing of the Claims. New claim 31 has been added. As amended, the claims are supported by the specification and the original claims.

Specifically the amendment of claim 20 is supported in the specification at p. 2, ll. 5-7 ("...preferably a peptide ... antibacterial *per se*, which can penetrate, and damage, the bacterial cell wall..."), p. 4, ll. 4-7 ("[t]his transport mediator is preferably a compound which as such is already detrimental to the prokaryote, e.g. by damaging the membranes (e.g. by forming pores or lesions)...preferably defensins or holins..."), in addition to p. 3, l. 26 to p. 4, l. 2 and p. 4, ll. 9-13, and the claims as originally filed. Such an amendment is made to clarify that the phage-holin portion of the conjugate is able to penetrate the entire cell, including both the external cell wall and the cellular membrane.

Claims 21, 22, 24, 27, and 27 have been amended to clarify those claims.

No new matter has been added, as defined by 35 U.S.C. § 132.

Thus, upon entry of the amendments, claims 20-27, 29, and 30-31 will be pending and under examination.

Rejection of claims 20-27, 29 and 30 under 35 U.S.C. §103(a)

In the Office Action mailed February 26, 2008 the Examiner has rejected claims 20-27, 29 and 30 as obvious under 35 U.S.C. §103(a) in light of U.S. Patent No. 6,548,651 (hereinafter Nielsen et al.), Good et al., *Nature Biotechnology*, vol. 19:360-364, April 2001 (hereinafter Good et al.), and PCT Application No. WO/1998/52614 (hereinafter Rothbard et al.), in view of Oki et al., *Gene*, vol. 197:137-145, April 16, 1997(hereinafter Oki et al.), Good et al., *Nature Biotechnology*, vol. 16:35-358, April 1998 (hereinafter Good et al. (2)), and U.S. Patent No. 6.821,948 (hereinafter Braun et al.). Applicants respectfully disagree.

The examiner described the provisions of the combined references Nielsen et al., Good et al., and Rothbard et al., concluding that "[t]he prior art discussed so far has taught all of the limitations

of the instant invention *except the use of phage-holin peptides as transport mediators*, the use of polylysine linkers and the specific PNA sequence of claim 12 [sic, claim 27]." (Office Action mailed February 26, 2008, p. 5; emphasis added.)

Oki et al. is cited by the examiner as showing "that phage holin proteins were known in the art and known to be cell wall penetrating proteins and antimicrobial." (Office Action mailed February 26, 2008, p. 5.) Applicants respectfully disagree that the combined references of Nielsen et al., Good et al., Rothbard et al. and Oki et al. describe the characteristics of the phage-holin proteins recited as an element of claim 20.

The examiner's attention is respectfully drawn to claim 20, as amended. The claim recites a conjugate comprising, in part "a phage-holin protein as transport peptide or protein adapted to penetrate the infectious prokaryote." The specification describes penetration by the transport protein portion of the conjugate at p. 2, ll. 5-7, describing penetration of the cell wall, p. 4, ll. 4-7, describing damage of the cell membranes, and p. 3, l. 26 to p. 4, l. 2 and p. 4, ll. 9-13, and the claims as originally filed, describing cell membrane penetration. Clearly the phage-holin protein portion of the claimed conjugate mediates entry of the conjugate through both the external cell wall and the prokaryotic cellular membrane.

Oki et al. describe release of progeny particles from a host cell. Accordingly the process described in Oki et al. involves phages starting on the inside of a cell, working their way out. In describing this process, Oki et al. state that "the cell lysis has been presumed to depend upon phage-encoded proteins: *e.g.* holin and endolysin. Holins have been thought to form a hole in the cytoplasmic membrane, through which endolysin can attack the peptidoglycan layer." (page 137, 2nd col, 1st para.) Oki et al. therefore maintain that cell lysis depends upon the presence of holin and endolysin. As described, beginning internally, holin forms a hole in the inner cytoplasmic membrane, through which endolysin can gain access to and attack the peptidoglycan layer of the outer cell wall.

The authors of Oki et al. characterized the properties of holin in *E. coli*, including a comparison of cell state following individual and co-expression of the *hol* and *lys* genes. The results of expression of *hol* alone "yielded translucent (empty ghost) cells…[where]…[t]he cytoplasmic membranes of these ghost cells were disrupted locally and severely, whereas the cell walls seemed to remain almost normal" (p. 139, 2nd col., para. 2.2). The cells resulting from expression of *hol* alone are described as "the bulk of the cell wall [is] undisturbed…" (Abstract, emphasis

added), and expression of *lys* "alone caused curling up of the cell wall on the bulge" but co-expression of *hol* and *lys* "led to substantial changes in both cytoplasmic membrane and cell wall..." (p. 139, 2nd col., para. 2.2)

Oki et al. therefore do not describe, as suggested by the examiner, that phage-holin proteins can translocate through a bacterial cell wall. Instead, Oki et al. show that holin forms a pore in the inner cell membrane of *E. coli*, allowing lysin to gain access to the outer cell wall, but holin alone was shown to not disrupt the cell wall.

In considering a reference for its effect on patentability, the reference is required to be considered in its entirety, including portions of teach away from the invention under consideration. Simply stated, the prior art must be considered as a whole. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); MPEP § 2141.02. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *Application of Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 796 F.2d 443, 448 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987).

Furthermore, in *KSR International Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. ___ (2007), the Supreme Court confirmed that references that teach away from the invention are evidence of the non-obviousness of a claimed invention, (*KSR*, slip op. at pp. 20-23) and reaffirmed the principle that a fact finder judging patentability "should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."

Applicants therefore assert that Oki et al. teach away from the claimed invention by the demonstration that holin affirmatively does not disrupt the cell wall, in contrast to the recitation in claim 20 of a phage-holin protein as a "transport protein adapted to penetrate the infectious prokaryote."

Furthermore, Good et al. demonstrate that the *E. coli* outer cell wall is a major barrier to PNAs and that cell wall permeabilizing peptides are necessary for a peptide-mediated delivery of PNA into bacteria (page 361, 2nd para.).

Therefore the combined references of Nielsen et al., Good et al., Rothbard et al. and Oki et al. do not provide a showing of a conjugate, as claimed, and teach away from the claimed conjugate

containing a phage-holin protein as a transport peptide or protein adapted to penetrate the infectious prokaryote. The additionally cited references Good et al (2) and Braun et al. do not remedy the deficiencies.

A person of skill in the art, with knowledge of the combination of references Nielsen et al., Good et al., Rothbard et al., Oki et al., Good et al (2) and Braun et al. would not have been motivated to choose a phage-holin protein as mediator for the transport of a bactericidal PNA into bacteria, because Oki et al. do not teach or suggest that a phage-holin protein is capable of translocating a compound across the bacterial cell wall. Oki et al. clearly report that a two-component system consisting of a holin for disrupting the inner cell membrane and lysin for attacking the outer cell wall are necessary, but holin alone was shown to not disrupt the outer cell wall. Viewed in this light, a person of skill in the art would not have a reasonable expectation of success that a conjugate comprising a phage-holin protein and a bactericidal PNA would be translocated via the cell wall into a prokaryote, because when considering Good et al. the person of skill would know that the *E. coli* outer cell wall is a major barrier to PNAs and that a transport protein or peptide would be needed, but that in view of Oki et al. a compound in addition to holin would be necessary to penetrate that outer cell wall. Therefore, in light of the cited references, one of skill in the art would not have been motivated to make the claimed conjugate. Thus, the conjugate recited in independent claim 20 (and in new claim 31) is not obvious in light of the cited references.

As Nielsen et al., Good et al., and Rothbard et al., in light of Oki et al., Good et al (2) and Braun et al. do not provide any logical basis for the conjugate recited in claims 20-27, 29 and 30 (and new claim 31), Nielsen et al., Good et al., and Rothbard et al., in light of Oki et al., Good et al (2) and Braun et al. do not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 20-27, 29 and 30 under 35 U.S.C. § 103 (a) as being obvious over Nielsen et al., Good et al., and Rothbard et al., in light of Oki et al., Good et al (2) and Braun et al. is respectfully requested.

Fees Payable for Added Claims

By the present Amendment, 1 new independent claim has been added. The number of claims in the present application is now 2 independent claims and 11 total claims. Accordingly, the total number of pending claims does not exceed the amount of 3 independent and 20 total allowed by

payment of the initial filing fee. No additional fees are due in conjunction with the addition of claim 31 in the present Response.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 20-27, 29-31 are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the February 26, 2008 Office Action without extension was set at three months, or May 26, 2008. Applicants hereby request a two month extension of time under 37 C.F.R. § 1.136. Payment of the extension fee of $230.00 specified in 37 C.F.R. § 1.17(a)(2), as applicable to small entity, is being made by on-line credit card payment at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

Date: July 28, 2008

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